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FUNCTIONAL INVESTIGATION OF THE HUMAN OOCYTE-EXPRESSED GENE BCAR4 USING DOMESTIC ANIMAL MODELS AND GENOME EDITING

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We have previously characterized BCAR4 (Breast Cancer Anti-estrogen Resistant 4) as a gene preferentially expressed in human oocytes as compared to ovarian somatic cells or non-pathologic non-reproductive tissues. BCAR4 is conserved in primates and in various domestic species such as cow, pig, dog, horse or rabbit, but it is not found in the genome of rodents. This pattern coincides with a delayed major activation of the embryonic genome, i.e. after several cleavages. BCAR4 is also an oncogene overexpressed in a subset of breast tumors and other cancers. Altogether, the restricted expression, proliferative properties and phylogeny suggested that BCAR4 may be involved in early embryonic divisions. We have analyzed BCAR4 expression in the cow. While RNA is already transcribed in the oocyte of preovulatory follicles, protein synthesis is delayed until late maturation, peaks in early cleaving embryos, persists until the morula stage to become undetectable in blastocysts. Microinjecting BCAR4-targeting small-interfering RNA significantly decreased BCAR4 expression and compromised in vitro blastocyst development, demonstrating that BCAR4 is a maternal-effect gene. To investigate BCAR4 function in vivo, the rabbit model was chosen for genome editing. Rabbits carrying an altered BCAR4 gene were produced using a transcription activator-like effector nuclease (TALEN). Wild-type, heterozygous and homozygous carrier animals were born following the expected mendelian ratio. They were viable and appeared healthy, as expected for animals with an altered maternal effect-gene. Efficiency of the genetic alteration was evaluated by reverse-transcription coupled to PCR. It showed that BCAR4 RNA expression was abolished in follicles from homozygous carriers as compared to their heterozygous and wild-type littermates. These females will be phenotyped onto various reproductive parameters to assess the role of BCAR4 in fertility in vivo.